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**(54) Title:** CLEAR NON-ALCOHOLIC HYDROCORTISONE SOLUTIONS**(57) Abstract**

This invention relates to clear aqueous solutions of hydrocortisone which are free of lower alcohols. When applied to the skin, either directly or by wipe, the solution is practically invisible and has a further advantage that the solution will not irritate or dry the skin or give the stinging sensation of an alcohol-containing solution. Dissolution of hydrocortisone without alcohol is accomplished by using the anionic surfactant sodium dioctyl sulfosuccinate in mixtures of glycerin, propylene glycol and polyethylene glycol diluted to final volume with water.

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## CLEAR NON-ALCOHOLIC HYDROCORTISONE SOLUTIONS

### Field of Invention

This invention relates to clear alcohol-free hydrocortisone compositions which are useful for external treatment of skin irritations, itching, and rashes. The solubilization of hydrocortisone in a mixture of non-volatile organic co-solvents is accomplished by adding the anionic surfactant sodium dioctyl sulfosuccinate (docusate sodium). The product can be applied to the skin as a liquid or gel or with towelettes or wipes pre-moistened with an invention hydrocortisone solution. Hydrocortisone is approved in up to a one percent concentration for non-prescription pharmaceutical products.

### Background of the Invention

Hydrocortisone is used in many topical preparations as a treatment for temporary relief of itching associated with minor skin irritation, inflammation and rashes due to eczema, insect bites, poison ivy, poison oak, poison sumac, soaps, detergents, cosmetics, seborrheic dermatitis, psoriasis and itching in the genital and anal areas of the body. Hydrocortisone has very little solubility in water, only 28 mg of hydrocortisone per 100 ml of water (Merck Index, Eleventh Edition). Because of the limited solubility of hydrocortisone in water (0.028% on a weight/volume basis), it is necessary to add co-solvents, surfactants, and/or complexing agents to obtain an aqueous solution of hydrocortisone in sufficient concentration so as to be useful in treating the conditions for which topical hydrocortisone is indicated. Hydrocortisone is often formulated as a suspension or emulsion in the form of a lotion or cream base which may not be permanently homogeneous.

Because of the low solubility of hydrocortisone, preparation of clear solutions of hydrocortisone at 1-2% concentrations is difficult. Co-solvents such as a lower molecular weight alcohol (ethyl alcohol, isopropyl alcohol) may be added to increase solubility or surfactants may be added to form emulsions of the oil-in-water or water-in-oil type. U. S. Patent 2,880,130 discloses the use of polyoxyethylene sorbitan monooleate (Tween 80®) in amounts of from 2-25 percent of the vehicle to obtain clear aqueous solutions containing up to 0.2% of hydrocortisone. U. S. patent 4,289,764 describes formulations containing 0.025 to 0.4% hydrocortisone in an aqueous 15-50% propylene glycol solution acidified to pH 2.7-3.3 with a non-toxic organic acid such as citric acid. U. S. patent 4,305,936 provides for a 0.005-2.5% hydrocortisone clear liquid formulation containing 1-4% by weight of a glyceryl ester of fatty acids having 6-22 carbon atoms, 1-3% by weight of the hydrocortisone of a betaine surfactant, and 10-50% of an alkanol co-solvent, preferably ethanol. U. S. patent 4,778,060 describes a 0.5% hydrocortisone aqueous solution for use as a douche and for impregnating towelettes for wipes. The solution also contains

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caprylic/capric triglycerides (5-20%), sorbitan stearate (2-4%), Polysorbate 60® (1-3%), preservatives and citric acid.

U. S. patent 4,383,992 discloses an aqueous solution of an inclusion complex of unbranched beta-cyclodextrin and hydrocortisone and reveals that the inclusion complex must dissociate before the hydrocortisone is physiologically active. U. S. patent 5,229,370 discloses an aqueous solution on an inclusion complex composed of a branched beta-cyclodextrin and hydrocortisone. The branched beta-cyclodextrin inclusion complex appears to incorporate greater amounts of hydrocortisone than the unbranched beta-cyclodextrin of the previous patent.

The unexamined Japanese patent application JP 05170643 discloses micellar ophthalmic preparations containing 0.5-1.0% water insoluble steroid, a non-ionic surfactant, polyalcohols and water.

V. Das Gupta, *Drug Development and Industrial Pharmacy* 11(12), 2083-2097 (1985) reported that the anionic surfactant sodium lauryl sulfate adversely affected the stability of hydrocortisone solutions in aqueous ethanolic solutions of hydrocortisone also containing glycerin and/or propylene glycol.

### Summary of the Invention

The invention provides hydrocortisone solutions free of lower alcohols such as ethanol, propanol or isopropanol for topical use and a process for preparation of the alcohol-free solutions. An alcohol free preparation is less likely to irritate or dry the skin or burn when applied at the affected area of the skin. The invention also provides for hydrocortisone solutions which are colorless and thus are less visible on the skin than non-colorless preparations. The invention further provides for hydrocortisone solutions which are stable and homogenous and which have a pH that is compatible with the skin in a human.

The invention solutions of hydrocortisone can be applied externally to the skin as a liquid by rubbing the liquid composition on the skin or applying the hydrocortisone solution with an applicator such as a spongy material, a roll-on applicator, a spray or a hydrocortisone solution-impregnated absorbent wipe. Wipes are conveniently prepared by impregnating a soft tissue such as a rayon web bonded with an acrylic copolymer binder or a 60% wool pulp, 30% rayon, 10% polyester/polyethylene blend with a clear alcohol-free solution of hydrocortisone according to the present invention. Formulation of the invention solution into a gel or more viscous solution for convenience in application is contemplated. The viscosity of the solution can be increased by adding to the solution one or more thickening adjuvants known in the art such as an acrylic acid polymer, hydroxyethylcellulose, hydroxypropylcellulose and the like. Incorporation of a fragrance in the invention composition is also contemplated. Further contemplated is addition of

effective amounts of approved topical dermatological agents. These agents comprise an antibiotic such as polymixin B sulfate, bacitracin zinc or neomycin sulfate to prevent or alleviate infection, an antihistamine such as benadryl to alleviate itching, a topical anesthetic such as zylocaine or benzocaine to alleviate pain or a sunscreen to protect the treated area of the skin from ultraviolet light damage. Such additives would aid in reducing discomfort due to swelling and itching and pain and help in treating or preventing skin infection.

### Detailed Description of the Invention

The clear lower alcohol-free hydrocortisone solutions of this invention are comprised of up to 2% hydrocortisone, 15-30% polyethylene glycol 1300-1600 MWR, 15-30% propylene glycol, 5-20% glycerin, 3-12.4% sodium dioctyl sulfosuccinate, buffers, preservatives and water to make up to 100%. Micronized hydrocortisone is preferred as the smaller particle size provides for more rapid dissolution.

The amount of micronized hydrocortisone is preferably 1% w/v, the maximum concentration currently allowed in non-prescription hydrocortisone products. Citric acid and sodium citrate at 0.2% w/v each are used to buffer the solutions at about pH 4.9-5.4. Preservatives are selected from methylparaben, propylparaben, sodium benzoate, Glydant®, Phenoxetol®, Phenonip®, benzalkonium chloride and benzyl alcohol. The anionic surfactant sodium dioctyl sulfosuccinate, preferably the composition identified as Monowet MO-84 R2W® (MONA Industries, Patterson, New Jersey) which contains 16% by weight of propylene glycol, is effective in facilitating solution of hydrocortisone in polyethylene glycol, propylene glycol and glycerin mixtures. The following examples are included to illustrate the various formulations useful in this invention and the processes for their preparation. These examples are included for illustrative purposes only and are not to be construed as limiting to this disclosure in any way. In the following examples certain ingredients are identified by trade names and are identified as follows:

Phenoxetol® is 2-phenylethanol.

Phenonip® is a mixture comprised of 2-phenoxyethanol (>70%), methyl p-hydroxybenzoate (>15%), ethyl p-hydroxybenzoate (<5%), propyl p-hydroxybenzoate (<5%), and butyl p-hydroxybenzoate (<10%).

Methylparaben is methyl p-hydroxybenzoate.

Propylparaben is propyl p-hydroxybenzoate.

Polyethylene glycol is a polyoxyethylene polymer of the formula HO-(CH<sub>2</sub>CH<sub>2</sub>O)<sub>n</sub>-H commercially available in several molecular weight ranges from about 200 to over 8,000. The preferred polyethylene glycol is polyethylene glycol which has a molecular weight range (MWR) from about 1300 to about 1600.

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**Example 1**

RAW MATERIAL	%W/V
Hydrocortisone Micronized	1.00
Polyethylene Glycol 1300-1600 MWR	25.0
5 Propylene Glycol	25.8
Glycerin 99%	10.0
Sodium Dioctyl Sulfosuccinate	4.2
Methylparaben	0.150
Phenoxyetol	1.00
10 Citric Acid	0.200
Sodium Citrate	0.200
Water	q.s. to 100 ml

Place the polyethylene glycol, propylene glycol, and sodium dioctyl sulfosuccinate in a suitable mixing container equipped with a mixer. Adjust the temperature to 60-65°C.

15 Add and dissolve the micronized hydrocortisone in the polyethylene glycol/ propylene glycol/ sodium dioctyl sulfosuccinate mixture maintained at 60-65°C.

Concurrently, place the glycerin in a suitable mixing container equipped with a mixer. Adjust the temperature to 85°C.

20 Add and dissolve the methylparaben in the glycerin. Continue mixing until a clear solution is obtained. Cool to 50°C.

Add the methylparaben solution to the hydrocortisone solution.

Dissolve the sodium citrate and citric acid in water in about a 1% concentration and add the solution to the hydrocortisone solution.

Add the Phenoxyetol to the hydrocortisone solution.

25 Dilute the hydrocortisone solution to 100% volume with water. Continue mixing for ten minutes.

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**Example 2**

RAW MATERIAL	%W/V
Hydrocortisone Micronized	1.00
Polyethylene Glycol 1300-1600 MWR	25.0
5 Propylene Glycol	25.8
Glycerin 99%,	10.0
Sodium Dioctyl Sulfosuccinate	4.20
Methylparaben	0.150
10 Phenonip	0.50
Citric Acid	0.200
Sodium Citrate	0.200
Water	q.s. to 100 ml

15 Place the polyethylene glycol, propylene glycol and sodium dioctyl sulfosuccinate in a suitable mixing container equipped with a mixer. Adjust the temperature to 60-65°C.

Add and dissolve the micronized hydrocortisone in the polyethylene glycol / propylene glycol/ sodium dioctyl sulfosuccinate mixture maintained at 60-65°C.

Concurrently, place the glycerin in a suitable mixing container equipped with a mixer. Adjust the temperature to 85°C.

20 Add and dissolve the methylparaben in the glycerin. Continue mixing until a clear solution is obtained. Cool to 50°C.

Add the methylparaben solution to the hydrocortisone solution.

Dissolve the sodium citrate and citric acid in water at about a 1% concentration and add the solution to the hydrocortisone solution.

25 Add the Phenonip to the hydrocortisone solution.

Dilute the hydrocortisone solution to 100% volume with water. Continue mixing for ten minutes.

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**Example 3**

RAW MATERIAL	%W/V
Hydrocortisone Micronized	1.00
Polyethylene Glycol 1300-1600 MWR	25.0
5 Propylene Glycol	25.8
Glycerin 99%	10.0
Sodium Dioctyl Sulfosuccinate	4.20
Methylparaben	0.150
Benzyl Alcohol	1.00
10 Citric Acid	0.200
Sodium Citrate	0.200
Water	q.s. to 100 ml

15 Place the polyethylene glycol, propylene glycol and sodium dioctyl sulfosuccinate in a suitable mixing container equipped with a mixer. Adjust the temperature to 60-65°C.

Add and dissolve the micronized hydrocortisone in the polyethylene glycol/propylene glycol/ sodium dioctyl sulfosuccinate mixture maintained at 60-65°C.

Concurrently, place the glycerin in a suitable mixing container equipped with a mixer. Adjust the temperature to 85°C.

20 Add and dissolve the methylparaben in the glycerin. Continue mixing until a clear solution is obtained.

Add the methylparaben solution to the hydrocortisone solution.

Dissolve the sodium citrate and citric acid in water at about a 1% concentration and add the solution to the hydrocortisone solution.

25 Add the benzyl alcohol to the hydrocortisone solution.

Dilute the hydrocortisone solution to 100% volume with water. Continue mixing for ten minutes.

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**Example 4**

	RAW MATERIAL	%W/V
	Hydrocortisone Micronized	1.00
	Polyethylene Glycol 1300-1600 MWR	25.0
5	Propylene Glycol	25.8
	Glycerin 99%	10.0
	Sodium Dioctyl Sulfosuccinate	4.20
	Methylparaben	0.150
	Propylparaben	0.100
10	Phenoxyetol	1.00
	Citric Acid	0.200
	Sodium Citrate	0.200
	Water	q.s. to 100 ml

15 Place the polyethylene glycol, propylene glycol and sodium dioctyl sulfosuccinate in a suitable mixing container equipped with a mixer. Adjust the temperature to 60-65°C.

Add and dissolve the micronized hydrocortisone in the polyethylene glycol/propylene glycol/ sodium dioctyl sulfosuccinate mixture maintained at 60-65°C.

20 Concurrently, place the glycerin in a suitable mixing container equipped with a mixer. Adjust the temperature to 85°C.

Add and dissolve the methylparaben and propylparaben in the glycerin. Continue mixing until a clear solution is obtained.

Add the methylparaben/propylparaben solution to the hydrocortisone solution.

25 Dissolve the sodium citrate and citric acid in water at about a 1% concentration and add the solution to the hydrocortisone solution.

Add the Phenoxyetol to the hydrocortisone solution.

Dilute the hydrocortisone solution to 100% volume with water. Continue mixing for ten minutes.

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**Example 5**

RAW MATERIAL	%W/V
Hydrocortisone Micronized	1.00
Polyethylene Glycol 1300-1600 MWR	25.0
5 Propylene Glycol	25.8
Glycerin 99%	10.0
Sodium Dioctyl Sulfosuccinate	4.20
Methylparaben	0.200
Propylparaben	0.100
10 Benzyl Alcohol	1.00
Citric Acid	0.200
Sodium Citrate	0.200
Water	q.s. to 100 ml

15 Place the polyethylene glycol, propylene glycol and sodium dioctyl sulfosuccinate in a suitable mixing container equipped with a mixer. Adjust the temperature to 60-65°C.

Add and dissolve the micronized hydrocortisone in the polyethylene glycol/ propylene glycol/ sodium dioctyl sulfosuccinate mixture maintained at 60-65°C.

20 Concurrently, place the glycerin in a suitable mixing container equipped with a mixer. Adjust the temperature to 85°C.

Add and dissolve the methylparaben and propylparaben in the glycerin. Continue mixing until a clear solution is obtained. Cool to 50°C.

Add the methylparaben/propylparaben solution to the hydrocortisone solution.

25 Dissolve the sodium citrate and citric acid in water at about a 1% concentration and add the solution to the hydrocortisone solution.

Add the benzyl alcohol to the hydrocortisone solution.

Dilute the hydrocortisone solution to 100% volume with water. Continue mixing for ten minutes.

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**Example 6**

RAW MATERIAL	%W/V
Hydrocortisone Micronized	1.50
Polyethylene Glycol 1300-1600 MWR	25.0
5 Propylene Glycol	26.12
Glycerin 99%	10.00
Sodium Dioctyl Sulfosuccinate	5.88
Methylparaben	0.20
Sodium Citrate	0.20
10 Citric Acid	0.20
Water	q. s. to 100 ml

The 1.5% hydrocortisone formulation is prepared by following the same sequences of procedures as given in Examples 1-5.

15

**Example 7**

RAW MATERIAL	%W/V
Hydrocortisone Micronized	2.00
Polyethylene Glycol 1300-1600 MWR	25.0
20 Propylene Glycol	27.40
Glycerin 99%	10.00
Sodium Dioctyl Sulfosuccinate	12.4
Methylparaben	0.20
Sodium Citrate	0.20
25 Citric Acid	0.20
Water	q. s. to 100 ml

The 2.0% hydrocortisone formulation is prepared by following the same sequences of procedures as given in Examples 1-5.

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Those skilled in the art of formulation will realize that still other formulations containing hydrocortisone and sodium dioctyl sulfosuccinate may provide clear solutions of hydrocortisone. Other preservatives including, but not limited to sodium benzoate, benzalkonium chloride and DMDM hydantoin [1, 3-bis(hydroxymethyl)-5,5-dimethyl-2,4-diazolidinedione] may also be used effectively.

The solutions prepared in the preceding examples remain clear on standing at room temperature.

**What is claimed is:**

1. A clear alcohol-free pharmaceutical composition comprised of hydrocortisone, dioctyl sodium sulfosuccinate, propylene glycol, polyethylene glycol, water, optional preservatives and/or buffers and optional thickeners, fragrances, and topical dermatological agents including antibiotics, antihistamines, anesthetics and sunscreens.
- 5 2. A composition according to claim 1 wherein the hydrocortisone content is one percent of the total weight.
3. A composition according to claim 1 wherein the hydrocortisone content is 1.5 percent of the total weight.
- 10 4. A composition according to claim 1 wherein the hydrocortisone content is 2.0 percent of the total weight.
5. A composition according to claim 1 wherein the composition is comprised of 1% micronized hydrocortisone, 15-30% polyethylene glycol 1300-1600 MWR, 15-30% propylene glycol, 5-20% glycerin 99%, 3-15% sodium dioctyl sulfosuccinate, citric acid and sodium citrate buffers, preservatives, and water to make up to final volume.
- 15 6. A composition according to claim 5 wherein the composition is comprised of 1% hydrocortisone micronized, 20-25% polyethylene glycol 1300-1600 MWR, 20-30% propylene glycol, 10% glycerin (99%), 5% sodium dioctyl sulfosuccinate, citric acid and sodium citrate buffers, preservatives selected from methylparaben, propylparaben, phenoxyethanol, or benzyl alcohol; and water to make up to final volume.
- 20 7. A process for preparing a composition according to claim 1 which comprises dissolving hydrocortisone, preferably micronized hydrocortisone, in a mixture of polyethylene glycol 1300-1600 MWR, propylene glycol, and sodium dioctyl sulfosuccinate, preferably at a temperature maintained at 60-65°C, adding thereto glycerin, or a mixture containing one or more of the preservatives methylparaben, propylparaben, or Phenonip dissolved in glycerin prepared at 80-85°C and subsequently cooled to about 50°C, adding to the combined solutions the citric acid and sodium citrate as about 1% solutions in water, and then adding to the combined solutions phenoxetol or benzyl alcohol if used and thickeners, fragrances, and topical dermatological agents, followed by adding sufficient water to make up to the final volume.
- 25 8. A wipe for treatment of dermatological conditions comprised of a tissue impregnated with a composition according to claim 1.
9. A wipe according to claim 7 which is selected from a rayon web bonded with an acrylic copolymer binder or a tissue comprised of 60% wool pulp, 30% rayon, and 10% polyester/polyethylene.
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## INTERNATIONAL SEARCH REPORT

1	Application No
PCT/US 95/16462	

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 A61K31/57 A61K47/20 A61K47/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,26 06 516 (DERMAL LABORATORIES) 2 September 1976 see claims 1,2 ---	1-9
A	EP,A,0 539 215 (STAFFORD-MILLER) 28 April 1993 see page 3, line 27 - line 33 see page 3, line 47 - page 4, line 15 ---	1-9
A	EP,A,0 179 583 (MERCK AND CO.) 30 April 1986 see claims 1,2,9 -----	1-9

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Date of the actual completion of the international search  10 April 1996	Date of mailing of the international search report  26.04.96
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## INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DE-A-2606516	02-09-76	GB-A-	1543907	11-04-79
		AU-B-	502937	16-08-79
		AU-B-	1123276	25-08-77
		FR-A,B	2341317	16-09-77
		JP-C-	1288963	14-11-85
		JP-A-	51106713	21-09-76
		JP-B-	60009486	11-03-85
<hr/>				
EP-A-539215	28-04-93	AU-B-	658681	27-04-95
		AU-B-	2726692	29-04-93
		CA-A-	2081269	24-04-93
		JP-A-	6128176	10-05-94
		NZ-A-	244862	26-07-95
<hr/>				
EP-A-179583	30-04-86	AU-B-	4825285	10-04-86
		JP-A-	61091117	09-05-86
<hr/>				